CHAPTER 3
Use of imaging in multiple sclerosis

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Introduction

Conventional magnetic resonance imaging (cMRI) has proven to be sensitive for detecting multiple sclerosis (MS) lesions and their changes over time [1]. This exquisite sensitivity has made cMRI the most important paraclinical tool in supporting a diagnosis of MS and establishing a prognosis at the clinical onset of the disease. These are the main reasons why cMRI findings have a major role in the International Panel (IP) diagnostic criteria for MS proposed during the past few years [2, 3]. Many research groups have subsequently taken steps to validate and refine these recommendations. However, for clinicians, it still remains unclear how and when cMRI should be used, not only at the onset of the disease, but also during the subsequent disease phases. In addition, despite the sensitivity of cMRI for detecting MS lesions, the correlation between cMRI metrics (i.e. hyperintense lesions on T2- and post-contrast T1-weighted images, hypointense lesions on T1-weighted images and atrophy measurements) and clinical findings of MS is still limited [1]. Among the likely reasons for this clinical/MRI discrepancy, a major one is the low pathological specificity of the abnormalities seen on cMRI scans and the inability of cMRI metrics to detect and quantify the extent of damage in normal-appearing brain tissues (NABT). These inherent limitations of cMRI have prompted the development and application of quantitative MR ‘non-conventional’ techniques (MR spectroscopy [1H-MRS], magnetization transfer [MT] MRI, diffusion weighted [DW] MRI and functional MRI [fMRI]) to the study of MS. Although these techniques have provided important insight into the pathobiology of MS, their practical value in the assessment of MS patients in clinical practice has yet to be realized.

Aim of the European Federation of Neurological Society (EFNS) task force

The aim of the ‘EFNS Expert Panel of Neuroimaging of MS’ is to define guidelines for the application of conventional and non-conventional MR techniques for the diagnosis and monitoring of patients with MS in clinical practice. In addition, they review the current status and clinical role of non-conventional MR techniques. The present guidelines are an update and a revision of the previous ones, which were published in 2006 [4].

Search strategy: data for this review were identified by searches of MEDLINE and references from relevant articles from 1965 to August 2009. The search terms ‘multiple sclerosis’, ‘magnetic resonance imaging’, ‘diagnosis’, ‘prognosis’, ‘atrophy’, ‘magnetization transfer MRI’, ‘diffusion weighted MRI’, ‘diffusion tensor MRI’, ‘proton magnetic resonance spectroscopy’, ‘disability’ and ‘treatment’ were used. Only papers published in English were reviewed.
MRI assessment of patients at presentation with clinically isolated syndromes suggestive of MS

In about 85% of patients with MS, the clinical onset of the disease is a clinically isolated syndrome (CIS) involving the optic nerve, brainstem, or spinal cord [5]. Approximately 50–80% of these patients already have lesions on cMRI, consistent with prior disease activity [6–8]. As several randomised controlled trials [9–12] have shown a treatment effect in patients with a CIS and MRI abnormalities suggestive of MS, it has become critical to expedite the identification of those patients with a high risk for developing a multiphasic inflammatory demyelinating disorder consistent with MS. Equally compelling has been the desire to characterize those factors that have the ability to prospectively predict which patients will be at highest risk for rapid and substantial disability accrual.

Conventional MRI

Diagnosis

All of the diagnostic criteria proposed for MS [2, 3, 13, 14] require the demonstration of disease dissemination in space (DIS) and time (DIT). The central principle advanced in each of these diagnostic schemes requires the confirmation of two or more clinical attacks, separated in time, which involve at least two distinct areas of the central nervous system (CNS). Another key requirement in each of the diagnostic criteria is the exclusion of alternative diagnostic considerations that can mimic MS by appropriate tests [15]. The Poser criteria, published in 1983, were the first set of criteria that integrated findings from paraclinical and laboratory tests (including cerebrospinal fluid [CSF] analysis, evoked potentials [EP] and MRI) to demonstrate spatial dissemination of the disease and to increase diagnostic confidence.

A critical feature in the diagnostic evaluation of patients suspected of having MS is the characterization of lesions profiles that are suggestive of the disease. Brain MS lesions are frequently located in the periventricular and juxtacortical white matter (WM) regions, the corpus callosum, and infratentorial areas (with the pons and cerebellum more frequently affected than the medulla and midbrain), and are sometimes characterized by oval or elliptical shapes [16]. Consensus has also been reached on criteria useful to identify T2-hyperintense [17] and T1-enhancing lesions [18]. Considering the frequent involvement of the spinal cord by MS, MRI features of MS cord lesions have also been identified [19]. Cord MS lesions are more frequently observed within the cervical than in other regions, are usually peripheral, limited to two vertebral segments in length or less, occupy less than half the cross-sectional area of the cord, and are not seen as T1-hypointensities. Acute plaques can produce swelling of the cord and enhancement after gadolinium (Gd) administration.

Recently, the application of a double-inversion recovery (DIR) sequence [20] has contributed to imaging lesions of the grey matter (GM). These lesions have been detected in the major disease clinical phenotypes, including those with CIS [21]. The sensitivity and utility of GM lesions detection in the context of MS diagnosis requires further investigation.

The optic nerve is also frequently involved in the course of MS. When an attack of optic neuritis (ON) is suspected to be the onset manifestation of MS, the principal role of MRI is to assess the brain for asymptomatic lesions [22–24], whereas optic nerve MRI can be useful in ruling out alternative diagnoses. The sensitivity of MRI for detecting optic nerve lesions in patients with ON is high: a seminal study using a short-tau inversion recovery (STIR) sequence showed lesions in 84% of symptomatic nerves and 20% of asymptomatic nerves [25]. The use of fat-saturated fast spin echo [26] and selective partial inversion recovery pre pulse (SPIR)-FLAIR [27] sequences has led to increases in sensitivity for detecting lesions in patients with an ON. In MS patients, increased T2 signal can be seen for a long time after an episode of ON, despite improvements in vision and visual EP, and even in the absence of acute attacks of ON [28]. T1-hypointense lesions are not usually seen in the optic nerve, whereas Gd enhancement is a consistent feature of acute ON [29].

A number of MRI criteria have been proposed [7, 30, 31] to increase the confidence in rendering a diagnosis of MS:

- **Criteria of Paty et al. [31]:** presence of at least four T2-hyperintense lesions, or three T2 lesions, of which one is periventricular. These criteria are characterized by high sensitivity but relatively low specificity [32] (Class I evidence).
- **Criteria of Fazekas et al. [30]:** presence of at least three T2-hyperintense lesions with two of the following...
characteristics: an infratentorial lesion, a periventricular lesion, and a lesion larger than 6 mm. These criteria showed both high sensitivity and high specificity when evaluated retrospectively in definite MS [33], but have limited predictive value when applied prospectively in patients with CIS [34] (Class II evidence).

- Criteria of Barkhof et al. [7]: presence of at least three of the four following features: at least one Gd enhancing lesion, at least one juxtacortical lesion, at least one infratentorial lesion, and three or more periventricular lesions (Class I evidence). In 2000, Tintorè et al. [35] slightly modified these criteria by allowing for nine T2 lesions to be an alternative for the presence of an enhancing lesion and reported a high specificity of these criteria to predict conversion from CIS to clinically definite (CD) MS (Class I evidence).

In 2001, an IP of MS specialists [2] proposed the use of MRI to generate objective evidence of lesion DIS and DIT. For the demonstration of DIS, the IP decided to apply the modified Barkhof-Tintorè criteria [7, 35]. When these imaging criteria were not fulfilled, the IP considered the presence of at least two T2 lesions plus the presence of oligoclonal bands in the CSF as equivalent. However, this alternative combination of criteria may result in a decreased diagnostic accuracy [36] (Class III evidence).

In the 2001 IP criteria [2], DIT can be demonstrated either by the presence of at least one enhancing lesion on an MRI scan performed 3 months or more after the onset of the clinical event or by the presence of one new T2 lesion which develops with reference to a prior scan obtained at least 3 months after the onset of the clinical event. The major advantage of the McDonald criteria is that they facilitate the early diagnosis of MS in patients with a clinically isolated attack before a second clinical relapse has occurred. Several studies have evaluated the ability of the IP criteria to predict conversion to CDMS and found a sensitivity ranging from 74 to 83% and a specificity of 83 to 85% [36, 37] (Class III evidence). Several studies have also assessed whether accurate pieces of information on DIS and DIT could be obtained with spinal cord MRI and serial T2-weighted images alone, respectively. The presence of asymptomatic cord lesions was found to contribute to the demonstration of DIS in recently diagnosed MS patients [38] (Class IV evidence), but the substitution of a brain lesion with a cord lesion did not impact significantly on the subsequent diagnosis in patients presenting with ON [39] (Class III evidence). When a new T2-lesion was allowed as evidence for DIT, one study showed that 82% of CIS patients who fulfilled the IP MRI criteria for MS after 3 months had developed CDMS within 3 years [39] (Class III evidence), and another found that 80% of those CIS who fulfilled the same criteria after 1 year developed CDMS within 3 years [36] (Class III evidence).

The IP criteria have been challenged by a consensus report of the Therapeutics and Technology Assessment Subcommittee of the AAN [40] that performed a systematic analysis of studies on the use of MRI in the diagnosis of MS and concluded that the presence of three WM lesions in CIS patients represents a more sensitive predictor of the subsequent development of CDMS than the IP criteria. The specificity of the IP criteria and of that proposed by the Subcommittee of the AAN [40] have been assessed in patients suspected of having MS, but who ultimately had another diagnosis [41]. Whereas the IP criteria for DIS had a good specificity (89%), those proposed by the Subcommittee of the AAN had a much lower specificity (29%), indicating an increased risk of a false-positive diagnosis (Class III evidence).

To simplify and make an even earlier diagnosis, while maintaining adequate sensitivity and specificity, the IP criteria have been revised recently [3] (table 3.1). The main changes derived from this revision pertain to: (a) the demonstration of DIT, which can be obtained by the detection of a new T2 lesion, if it appears at any time compared with a reference scan done at least 30 days after the onset of the first clinical event; (b) the use of spinal cord MRI to demonstrate DIS. In this context, a cord lesion can be considered equivalent to a brain infratentorial lesion, an enhancing cord lesion is equivalent to an enhancing brain lesion, and individual cord lesions can contribute together with individual brain lesions to reach the required number of T2 lesions; (c) the diagnosis of primary progressive (PP) MS, which can be made in the presence of typical clinical evolution when accompanied by suggestive MRI changes in both brain and spinal cord, even in the absence of positive CSF findings.

Meanwhile several proposals have been made to simplify the revised McDonald criteria. According to the Swanton criteria [42], at least one subclinical T2 lesion in at least two of four locations defined as characteristic for MS in the McDonald criteria (i.e. juxtacortical, periventricular, infratentorial, and spinal-cord) is required.
for DIS, while DIT requires a new T2 lesion on a follow-up scan irrespective of the timing of a baseline scan. Such interpretation can be done on T2-weighted images alone and does not require Gd enhancement. These criteria have been found to be slightly more sensitive (72%) than the original and revised McDonald criteria, while maintaining high specificity (87%) [42, 43] (Class II evidence). These criteria may lose differential diagnostic information, due to the absence of Gd administration. Recently, Rovira et al. [44] suggested that a single brain MRI study performed early (i.e. <3 months) after the onset of CIS is highly specific for predicting the development of CDMS in the presence of both Gd-enhancing and non-enhancing lesions, which, when present, suggest DIT (Class II evidence).

Individuals without overt clinical symptoms but with MRI features highly suggestive of MS (i.e. subclinical demyelinating lesions) have been recently defined ‘radiologically isolated syndromes’ (RIS). Although routinely encountered in clinical practice, only limited data exist on the natural history or evolution of such individuals. Okuda et al. acquired MRI data from 41 RIS subjects [45]. While radiologic progression was identified in 59% of the cases, only 10 patients converted to either CIS or CDMS [45]. The presence of Gd-enhancing lesions on the initial MRI was predictive of DIT on repeat imaging of the brain [45]. During a mean follow-up of 5.2 years, the rate of clinical conversions of 70 RIS patients who had DIS on MRI was 33% [46] (Class II evidence). Examination of pejorative markers for clinical conversion showed that sex, number of T2 lesions, presence of oligoclonal bands, and IgG index were not statistically different in patients with MS determined by MRI compared with CDMS [46]. Visual evoked potential abnormalities, young age, and Gd enhancement on follow-up MRI scans more frequent in CDMS than in MS determined by MRI [46].

### Prognosis
Several authors have investigated the prognostic role of MR-derived metrics in patients presenting with CIS. The MRI findings that showed the strongest predictive value for the subsequent development of CDMS on short- to medium-term follow-up were the number and extent of T2-visible brain lesions at disease onset [6, 8, 22, 47] (Class II evidence), the presence of infratentorial lesions [47] (Class III evidence) and the presence of Gd-enhancing lesions [7] (Class I evidence), [9] (Class IV evidence). For patients with CIS and brain MRI lesions, the chance of developing CDMS was > 80% over the next 14–20 years, in the longest follow-up study to date [8, 22]. Several studies also showed the baseline MRI pattern is a strong predictor of disability accumulation over time in these patients [8, 48] (Class IV evidence).

<table>
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<tr>
<th>Diagnostic criteria for multiple sclerosis: 2005 revisions to the ‘McDonald Criteria’ [3].</th>
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<tr>
<td><strong>Dissemination in space</strong></td>
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<td>Three of the following:</td>
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<td>- at least 1 Gd-enhancing lesion or 9 T2 lesions</td>
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<tr>
<td>- at least 3 periventricular lesions</td>
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<td>- at least 1 juxtacortical lesion</td>
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<tr>
<td>- at least 1 infratentorial lesion</td>
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<tr>
<td>A spinal cord lesion equivalent to a brain infratentorial lesion; can contribute along with individual brain lesions to reach required lesion number</td>
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<tr>
<td><strong>Dissemination in time</strong></td>
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<td>(a) Detection of Gd enhancement at least 3 months after onset of initial clinical event (if not at site of event)</td>
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<tr>
<td>(b) Detection of a new T2 lesion if it appears at any time compared to a reference scan done at least 30 days after onset of initial clinical event</td>
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<td><strong>Diagnosis of MS in disease with progression from onset</strong></td>
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<td>(a) One year of disease progression (retrospectively or prospectively determined).</td>
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<td>(b) Plus two of the following</td>
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<td>- Positive brain MRI (nine T2 lesions or four or more T2 lesions with positive VEP)</td>
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<td>- Positive spinal cord MRI (two focal T2 lesions)</td>
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<td>- Positive CSF (isoelectric focusing evidence of oligoclonal IgG bands or increased IgG index, or both)</td>
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Gd = gadolinium, MS = multiple sclerosis, MRI = magnetic resonance imaging, VEP = visual evoked potentials, CSF = cerebrospinal fluid.
During the past decades, several quantitative MR techniques have been developed for the assessment of brain damage in patients with MS. Even if the application of these techniques in everyday clinical practice is, at the moment, still premature, as these techniques often require dedicated personnel and specific software for the analysis, it is likely that with augmented availability their use in clinical practice will increase.

The progressive development of brain and spinal cord atrophy is a well-known neuroimaging feature of MS [49]. Objective quantification of CNS atrophy has been recognized as a potentially useful marker of the destructive and irreversible components of MS-related tissue damage. Recent MRI studies have confirmed that irreversible tissue loss/damage occurs early in the course of the disease and it is likely that the extent of such irreversible tissue damage conveys important prognostic information. In CIS patients who evolved to MS, the development of regional or global brain atrophy over a period of up to 3 years [50–52], as well as progressive brain GM atrophy, was observed [50]. In CIS patients, a low dose of interferon (IFN) beta-1a given subcutaneously once a week has been shown to reduce the rate of brain atrophy by about 30% over 2 years [51]. Conversely, compared to normal controls, cord area was found to be only slightly reduced in patients presenting with CIS and an abnormal MRI scan, and cord area remained stable over 1 year after disease onset [53].

Non-conventional MRI
(1) MT-MRI. Reduced MT ratio (MTR) values have been detected in the normal-appearing WM (NAWM) and GM from patients at presentation with CIS [54–56]. While a seminal study suggested that the extent of these abnormalities might be an independent predictor of subsequent disease evolution [56], subsequent studies did not confirm this observation [44, 55]. No MT MRI abnormalities have been detected in the cervical cord of CIS patients [57].

(2) DT MRI. DT MRI has disclosed subtle abnormalities in the NAWM of CIS patients [58], which were not predictive of DIT (as defined by McDonald criteria) at 3 and 12 months [58]. Recently, a significant increase of GM diffusivity has been described in these patients, which was unrelated to clinical activity [59].

(3) 1H-MRS. Metabolic abnormalities, consisting of a reduction of the concentration of N-acetylasparate (NAA) of the whole brain [60] and in an increase of myo-inositol (mI) and creatine (Cr) in NAWM [61] have been shown in CIS patients, suggesting that widespread axonal pathology, glial injury, and an increase in cell turnover or metabolism are rather early phenomena in the course of the disease. Metabolic abnormalities in CIS patients have been found to be more pronounced in those patients with evolution to CDMS over a relatively short period of time [62].

(4) Functional MRI. Using fMRI, an abnormal pattern of movement-associated cortical activation has also been described in CIS patients within 3 months of disease onset [63, 64]. In a 1-year follow-up study of CIS patients [65], those who developed CDMS had a different motor fMRI response at first presentation when compared with those who did not, suggesting that, in CIS patients, the extent of early cortical reorganization following tissue injury might be a factor associated to a different disease evolution.

Recommendations
In patients at presentation with CIS suggestive of MS (i.e. neurological findings typically seen in the setting of MS), after appropriate exclusion of alternative diagnostic considerations that can mimic MS, the following recommendations should be considered.

(1) cMRI of the brain (dual-echo, FLAIR, and post-contrast T1-weighted scans) should be obtained as soon as possible in all patients presenting with an isolated demyelinating syndrome involving the CNS, not only to collect additional evidence for DIS, but also to exclude other possible neurological conditions. As suggested by the guidelines from the AAN [40], the finding in these patients of three or more T2-hyperintense lesions with the imaging characteristics underlined by the IP guidelines [2, 3] (Level A recommendation) and the presence of two or more Gd-enhancing lesions at baseline are sensitive predictors of the subsequent development of CDMS within the next 7–10 years (Level B recommendation).

(2) The presence of three or more WM lesions on brain T2-weighted MRI in patients suspected of having MS is not diagnostic, especially when their location and appearance is non-characteristic for demyelination. In this context, the IP criteria [2, 3] should be applied. Incidental WM lesions are not an infrequent observation even in
the young normal population. Note that with ageing (at least > 50 years) incidental WM lesions may also show progression [66] (Good Clinical Practice Point, GCPP).

(3) In the case of corticosteroid treatment, which is known to dramatically suppress Gd enhancement, one of the possible markers of inflammation, cMRI should be performed before treatment or, at least, 1 month after treatment termination (GCPP).

(4) cMRI of the spinal cord is useful in those circumstances when brain MRI is normal or equivocal, and in patients with non-specific brain T2-abnormalities (especially when older than 50 years), because, contrary to what happens for the brain, cord lesions rarely develop with ageing per se [67]. In patients presenting with a spinal cord syndrome, spinal cord MRI is highly recommended to rule out other conditions that may mimic MS, such as compressive lesions (GCPP).

(5) In patients with acute ON, although it will not always be required, MRI of the optic nerve can be useful in ruling out alternative diagnosis. In this case, STIR sequences should be used (GCPP).

(6) Follow-up MRIs are required to demonstrate DIT. In this perspective, the appearance of Gd-enhancing lesions 3 months after the clinical episode or new T2 or Gd-enhancing lesions 30 days after the clinical episode (and after a baseline MRI assessment) is highly recommended. Follow-up scans should be performed with the same machinery and scanning parameters, and identical slice positions are required for exact comparison (Level B recommendation). A scanner with at least 1.0 Tesla should be used to optimize image quality and tissue contrast.

(7) Repeat scanning beyond the two initial studies needs to be considered by the neurologist individually according to the clinical circumstances that are appropriate for each patient (is not routinely recommended as the disease becomes more likely to manifest clinically in the longer term [68]) (GCPP).

(8) Nephrogenic systemic fibrosis (NSF) is a medical condition that has come to be associated with exposure to the Gd [69, 70]. Normal renal function has to be confirmed prior to Gd administration (GCPP).

(9) Although non-conventional MRI techniques may provide essential and critical information about patients with CIS, and their application for monitoring treatment might provide a more accurate assessment of efficacy on inflammation, axonal protection, and demyelination/remyelination, their use in clinical practice is currently not recommended. All these techniques are yet to be adequately compared to cMRI for sensitivity and specificity in detecting tissue damage in MS and for predicting the development of MS and disability. At present, these quantitative techniques show differences at a group level, but do not allow inferences at an individual level (GCPP).

(10) In patients with insidious neurological progression over at least one year, PPMS [71] can be diagnosed reliably in the absence of positive CSF findings (when typical brain and spinal cord MRI changes are present). Even if in these patients a positive CSF finding increases the level of confidence for a diagnosis of MS, such a finding is not specific and may be commonly detected in patients with progressive myelopathies of other causes (GCPP).

### MRI in patients with CDMS

In patients with relapsing-remitting (RR) and secondary progressive (SP) MS, disease activity is detected five to 10 times more frequently on cMRI scans than with clinical assessment of relapses. This, coupled with the fact that cMRI provides objective and sensitive measures of disease activity, led to the use of cMRI as an established tool for assessing the natural history of MS progression and for monitoring response to treatment. In a clinical trial context, cMRI is used as a primary outcome measure in phase II studies, where serial scans (usually monthly) are acquired to detect disease activity (new or enlarged T2-lesion counts, total enhancing and new enhancing lesion counts, and enhancing lesion volume) [72]. In phase III trials, given the uncertainty of cMRI in predicting clinical benefit, surrogate imaging methods are used as secondary outcome measures to detect disease progression, usually on yearly scans, specifically in terms of increase in total T2-hyperintense lesion load [73].

### Conventional MRI

The cMRI sequences typically used for studying MS patients are dual-echo and post-contrast T1-weighted scans. Lesion burden on T2 MRI increases by about 5–10% per year. Several cross-sectional studies evaluated differences in T2-lesion load among different MS phenotypes. T2-lesion load is higher in SPMS in comparison to benign, RRMS, and PPMS [74]. However, the magnitude of the correlation between T2-lesion measures and disability within various disease phenotypes in cross-sectional studies has been rather disappointing [75]. This poor relationship is likely related to the many limitations of the clinical scales used to measure impairment and disability in MS and to the inability of cMRI to characterize and quantify the extent and severity of MS pathology.
beyond T2-visible lesions [1]. Furthermore, albeit not confirmed by a subsequent study [76], a plateauing relationship between dual-echo lesion load and disability has been shown, indicating that for Expanded Disability Status Scale (EDSS) higher than 4.5, metrics different from T2-lesion loads should be taken into account [77]. Serial MRI studies have shown that enhancement occurs in almost all new lesions in patients with RRMS or SPMS and can be sometimes detected even before the onset of clinical symptoms [78]. The burden of MRI activity can be stratified on the basis of clinical phenotype, being higher in RRMS [79] and SPMS [80] in comparison with PPMS [80] and benign MS [79]. Severely disabled SPMS patients exhibit a substantially lower incidence of enhancing lesions when compared to those with mildly disabled RRMS [81]. Several studies have investigated the prognostic role of enhancing MRI on corresponding clinical parameters. The number of enhancing lesions increases shortly before and during clinical relapses and predicts subsequent MRI activity [82–84]. A moderate correlation has been demonstrated between the degree of clinical disability and the mean frequency of enhancing lesions in patients with RRMS [85] and SPMS [86].

A rigorous and valid strategy for the MR-based longitudinal monitoring of MS (either natural or modified by treatment) must involve the use of standardized imaging protocols (including consistency in slice thickness and imaging planes, field strength, and patient repositioning). Several guidelines have emphasized the importance of accurate patient positioning inside the magnet to define landmarks for achieving effective co-registration on serial scans. Such procedures facilitate the accurate interpretation of follow-up studies [73, 87]. Several reviews provide detailed analysis of the advantages and disadvantages of the application of different pulse sequences for characterizing the disease burden in MS [73]. In addition, considering the importance of active lesion detection for assessing disease activity, several strategies have been suggested to increase enhancing lesion detection, including increased post-injection delay, increased Gd dose, and the application of MT saturation pulses to reduce background signal and increase lesion identification [88]. However, despite the increased sensitivity of these strategies, the application of higher doses of Gd and MT pulsing in the routine assessment of MS patients is still not advisable due to an unfavourable cost-benefit ratio. On the contrary, there is general agreement that an interval of 5–7 min between the injection of contrast material and the acquisition of post-contrast sequences should be maintained routinely to optimize the sensitivity and create standardization within and between centres [89].

Over the past decade, a large number of parallel group, placebo-controlled, and baseline-versus-treatment trials have clearly shown the ability of several immunomodulating and immunosuppressive treatments to reduce both MRI-measured inflammation and the consequent increase of accumulated lesion burden in patients with CIS [9–12] (Class I evidence), RRMS [90–119] (Class I evidence) and SPMS [106, 120–125] (Class I evidence). The long-term effects of some of these treatments on MRI-accumulated disease burden have also been documented ([126–128] (Class I evidence). A few studies in patients treated with IFN-beta, have explored whether MRI disease activity measured with Gd or new T2 lesions at the beginning of the treatment identifies better subsequent therapeutic response than clinical activity [129–132] (Class I evidence). Patients with rapidly evolving severe RRMS, defined by two or more disabling relapses in one year, and with one or more Gd-enhancing lesions on brain MRI or a significant increase in T2 lesion load as compared to a previous recent MRI, have been shown to have a greater treatment effect in the natalizumab trial [102]. Following the European Medicines Agency (EME) guidelines, natalizumab is indicated as single disease modifying therapy in highly active RRMS for the following patient groups: (a) patients with high disease activity (including at least one Gd-enhancing lesion) despite treatment with an IFN-beta, or (b) patients with rapidly evolving severe RRMS (including new T2 lesions or at least one new Gd-enhancing lesion compared with a recent MRI). Even if these data suggest that MRI classification may facilitate rational therapeutic decisions, they need to be replicated before being applied in clinical practice.

Persistently hypointense lesions on enhanced T1-weighted images (known as ‘black holes’) correspond to areas where chronic severe tissue disruption has occurred. At present, there is a general tendency to consider the assessment of the extent of chronic black holes as a surrogate marker to monitor MS evolution. T1-hypointense lesion load is higher and increases more rapidly over time in SPMS and PPMS than in RRMS [133]. In addition, T1-hypointense lesion load correlates better with clinical disability than T2-lesion load, particularly in SPMS
patients. A few trials have investigated the effect of treatment in preventing the accumulation of T1 black holes [134–137] in RRMS and SPMS and have consistently shown that the effect, if any, of all the tested treatments in reducing the rate of accumulation of black holes is moderate at best. A greater effect has been shown in patients treated with natalizumab: median T1-hypointense lesion volume decreased by 1.5% in the placebo group and by 23.5% in the natalizumab group [102]. Several studies have also evaluated the effects of available treatments [138–140] on the probability of newly formed MS lesions to evolve into chronically T1-hypointense lesions. Although this approach is highly time-consuming, it is promising for assessing in a relatively short time the ability of a given treatment to favourably alter the mechanisms leading to irreversible tissue loss.

Measurement of brain and cord atrophy has also been applied to assess the extent of tissue loss in MS [49, 141]. In MS patients with different disease phenotypes, on average, brain volume decreases by about 1% yearly [49], despite evidence of highly variable disease activity. Although it appears to be more pathologically specific than T2-lesion load, brain atrophy is at best only moderately correlated with disability in RRMS and SPMS [49, 142]. The strength of the correlation increases when neuropsychological impairment is considered [143] and with a longitudinal study design [144, 145]. Also, in patients with MS, particularly in those with the progressive phenotypes of the disease, changes at a given time point and over time of cord cross-sectional area correlate better with clinical disability than changes in cord T2-visible lesions [19].

Good correlations have been found between regional brain atrophy and disability in MS patients. GM atrophy has been demonstrated by cross-sectional and longitudinal studies [146, 147] from the early stages of the disease. Such a GM atrophy tends to worsen over time [148], and is correlated with worsening of disability progression [149]. In addition, brain atrophy appears to evolve by involving different structures in different phases of the disease, with ventricular enlargement predominant in RRMS and cortical atrophy more important in the progressive forms of the disease [150, 151].

As shown for T1-hypointense lesions, the effect of treatment in preventing the development of brain atrophy in patients with RRMS and SPMS was at best moderate and not seen at all in some studies [84, 102, 121, 152–156]. Overall, treatment effects on T1-hypointense lesions are more impressive than those seen on brain atrophy and are more in line with treatment effects observed on T2 lesions. The T1 lesion putatively investigates axonal loss only in a subgroup of visible WM lesions; whereas whole brain atrophy will be sensitive to neuroaxonal loss wherever it occurs in brain GM or WM.

To refine the reproducibility of brain atrophy measurements, several recommendations have been provided [49, 142], including: (1) the acquisition of 3D T1-weighted sequences; (2) the use of automated segmentation algorithms for images segmentation; (3) the development of a quality assurance programme to confirm the stability of the measurement system over time.

Non-conventional MRI

MT-MRI, DT-MRI, and 1H-MRS provide quantitative and continuous measures that can assess global (whole brain) as well as specific CNS structures, including the optic nerve and spinal cord, and various compartments (i.e. macroscopic lesions, NABT, NAWM, and GM) [157–159]. Using these techniques, microscopic abnormalities beyond the resolution of cMRI have been detected in patients with different MS phenotypes and have been shown to correlate better with the degree of disability and cognitive impairment than cMRI measures [157–159]. Longitudinal studies have shown significant worsening of non-conventional MRI metrics over time in MS patients. These techniques provide useful prognostic information for the medium-term clinical disease evolution [160–162].

Although the optimization and standardization across multiple sites and over time of MT sequences might be challenging, and long-term longitudinal studies using MT MRI are lacking, MT MRI holds substantial promise to provide good surrogate measures for MS evolution. This is witnessed by the fact that several MS trials have already incorporated MT MRI quantities as additional outcome measures, with a view to assessing the impact of treatment on demyelination and axonal loss. MT MRI has been used in phase II and phase III trials for RRMS (injectable and oral IFN beta-1a, IFN beta-1b, and oral glatiramer acetate [GA]) and SPMS (IFN beta-1b and immunoglobulins). In these phase III trials, MT MRI acquisition has been limited to highly specialized MR centres and only subgroups of patients (about 50–100 per
CHAPTER 3 Imaging in multiple sclerosis

Recommendations
In patients with established MS, the following recommendations should be considered:

1. cMRI scans (dual-echo and post-contrast T1-weighted images) should be obtained using standardized protocols and accurate procedures for patients’ repositioning to facilitate the interpretation of follow-up studies. Post-contrast T1-weighted scans should be acquired after an interval of 5–7 min from the injection of contrast material. Considering the weak correlation with clinical finding and the low predictive value of cMRI metrics for the subsequent worsening of clinical disability, the use of surveillance MRI for the purpose of making treatment decisions cannot be generally recommended. Serial MRI scans should be considered when diagnostic issues arise (GCPP).

2. Repetition of MRI of the spinal cord is advisable only if suspicion arises concerning the evolution of an alternate process (e.g. mechanical compression) or atypical symptoms develop (GCPP).

3. Although preliminary work based on clinical trial data has suggested that the presence and amount of MRI-detected disease activity may identify IFN response status in terms of relapse rate and accumulated disability in MS patients at a group level, there are no validated methods for using monthly $^1$H-MRS scans, Sarchielli et al. [170] found that treatment with IFN beta-1a has an impact on Cho peaks in spectra of lesions from RRMS patients, suggesting an increase in lesion membrane turnover during the first period of treatment. Narayanan et al. [171] found an increase of NAA/Cr in a small group of RRMS patients after 1 year of treatment with IFN beta-1b, suggesting a potential effect of treatment in preventing chronic, sublethal axonal injury. Schubert et al. [172] showed a stability of metabolite concentration over time in patients with RRMS treated with IFN beta-1b. Khan and co-workers [173] showed that patients receiving GA therapy for 4 years had an increase in NAA in the NAWM. One study used multicentre $^1$H-MRS data to assess PPMS patients [174]. This study reported comparable cross-sectional $^1$H-MRS values in healthy controls from different centres, indicating that $^1$H-MRS data can be highly reproducible across sites, when factors such as data acquisition, position and size of the volume of interest, postprocessing, and quantification procedures are standardized. A 3-year follow-up [175] showed no significant difference in metabolite ratios between patients treated with GA and those of the placebo group in lesions, NAWM and GM. However, there were also no detectable temporal changes in metabolite ratios in the two groups of patients relative to baseline values during the study period. As a consequence, $^1$H-MRS sensitivity to MS-related changes in clinical trials remains to be established.

A panel of MS experts has recently reviewed the current clinical applications of $^1$H-MRS in MS, discussed the potential and limitations of the technique, and suggested recommendations for the application of $^1$H-MRS to clinical trials [176].
monitoring disease-modifying therapy in individual patients (Class I evidence).

(4) Metrics derived from cMRI are not enough to provide a complete picture of the MS pathological process. Although cMRI has undoubtedly improved our ability to assess the efficacy of experimental MS therapies and, at least partially, our understanding of MS evolution, it provides only limited information on MS pathology in terms of accuracy and specificity and it has limited correlations with clinical metrics. This implies that the ability of a given treatment to modify metrics derived from cMRI does not mean that the treatment will necessarily be able to prevent the progressive accumulation of clinical disability, especially at an individual patient level.

(5) Measurements of T1-hypointense lesions loads and brain and cord atrophy in clinical practice continue to be considered at a preliminary stage of development, as they need to be standardized in terms of acquisition and post-processing. Conversely, these metrics should be included as an end-point in disease-modifying agents trials, to further elucidate the mechanisms responsible for disability (GCPP).

(6) The application of non-conventional MRI techniques in monitoring patients with established MS in clinical practice is, at the moment, not advisable. All these techniques still need to be evaluated for sensitivity and specificity in detecting tissue damage in MS and its changes over time (GCPP).

(7) MT-MRI should be incorporated into new clinical trials to gain additional insights into disease pathophysiology and into the value of this technique in the assessment of MS (Class II evidence). The performance and contribution of DT MRI and 1H-MRS in multicentre trials still have to be evaluated.

Conflicts of interest
D. L. Arnold has served on advisory boards for Genentech and Biogen Idec, and received speaker honoraria from Genentech, MS Forum, Biogen Idec, Serono Symposia, Teva & Sanofi Aventis, Teva Neuroscience, Bayer HealthCare Pharmaceuticals, and EMD Serono. He has received consultant’s fees from Biogen Idec, Teva Neuroscience, MS Forum, Genentech, Bayer HealthCare Pharmaceuticals, Novartis, and Eisai Medical Research, and grants from Multiple Sclerosis Society of Canada and Canadian Institutes of Health Research.

R. Bakshi has received speaker honoraria and grants from Biogen Idec, Teva Neuroscience, and EMD Serono.

F. Barkhof has received consultancy fees from Bayer-Schering Pharma, Sanofi-Aventis, Biogen-Idec, UCB, Merck-Serono, Novartis, and Roche.

N. De Stefano has served on advisory boards for Merck-Serono and received speaker honoraria from Merck-Serono, Teva, Biogen, and Bayer. He has received a consultant’s fee from Merck-Serono and travel grants from Merck-Serono and Biogen.

F. Fazekas has served on advisory boards and received speaker honoraria from Biogen Idec, Sanofi-Aventis, Merck-Serono, and Bayer Schering. He has received grants from Bayer Schering, Biogen Idec, Teva Sanofi Aventis, Baxter, and Merck-Serono.

M. Filippi has received speaker honoraria and grants from Teva, Merck-Serono, Bayer Schering, Biogen-Dompé, and Genmab. He has received a consultant’s fee from Peppgen and travel grants from Teva, Merck-Serono, Bayer Schering, and Biogen-Dompè.

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References
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